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REVIEW ARTICLE
Genomewide Scans of Complex Human Diseases: True Linkage Is Hard to Find

Janine Altmüller,[1] Lyle J. Palmer,[3,4] Guido Fischer,[1] Hagen Scherb,[2] and Matthias Wjst[1]

Institutes of [1]Epidemiology and [2]Biomathematics and Biometrics, National Research Center for Environment and Health, Neuherberg, Germany; [3]Channing Laboratory, Brigham and Women's Hospital and Harvard Medical School, Boston; and [4]Department of Epidemiology and Biostatistics, Case Western Reserve University, Cleveland

Many "complex" human diseases, which involve multiple genetic and environmental determinants, have increased in incidence during the past 2 decades. During the same time period, considerable effort and expense have been expended in whole-genome screens aimed at detection of genetic loci contributing to the susceptibility to complex human diseases. However, the success of positional cloning attempts based on whole-genome screens has been limited, and many of the fundamental questions relating to the genetic epidemiology of complex human disease remain unanswered. Both to review the success of the positional cloning paradigm as applied to complex human disease and to investigate the characteristics of the whole-genome scans undertaken to date, we created a database of 101 studies of complex human disease, which were found by a systematic Medline search (current as of December 2000). We compared these studies, concerning 31 different human complex diseases, with regard to design, methods, and results. The "significance" categorizations proposed by Lander and Kruglyak were used as criteria for the "success" of a study. Most (66.3% [$n = 67$]) of the studies did not show "significant" linkage when the criteria of Lander and Kruglyak (1995) were used, and the results of studies of the same disease were often inconsistent. Our analyses suggest that no single study design consistently produces more-significant results. Multivariate analysis suggests that the only factors independently associated with increased study success are (*a*) an increase in the number of individuals studied and (*b*) study of a sample drawn from only one ethnic group. Positional cloning based on whole-genome screens in complex human disease has proved more difficult than originally had been envisioned; detection of linkage and positional cloning of specific disease-susceptibility loci remains elusive.

Introduction

Complex human diseases involve multiple, interacting genetic and environmental determinants (Weeks and Lathrop 1995). Many such diseases have increased in incidence during the past 2 decades in the developed nations and are of major clinical and economic significance. During the same period, the genetic etiology of many complex human diseases has been increasingly emphasized as a means of better understanding their pathogenesis, with the ultimate goal of improving preventive strategies, diagnostic tools, and therapies (Risch 2000). During the past decade, considerable effort and expense have been expended in whole-genome screens aimed at detection of genetic loci contributing to the susceptibility to complex human diseases.

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Address for correspondence and reprints: Dr. Janine Altmüller, Ingolstädter Landstrasse 1, D-85764 Oberschleissheim, Germany. E-mail: altmueller@gsf.de

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Positional cloning begins with the identification of a chromosomal region that is transmitted within families, along with the disease phenotype of interest (genetic linkage). Positional cloning has been extremely useful in the identification of genes responsible for diseases with simple Mendelian inheritance, such as cystic fibrosis (Zielenski and Tsui 1995). The ultimate goal of positional cloning is to identify sequence variants within the coding or controlling regions of a gene associated with the phenotype of interest. However, the success of such positional cloning attempts has been limited, and most of the fundamental questions relating to the genetic epidemiology of complex human disease remain unanswered. In contrast to what has been found for monogenic traits, the results have often been disappointing or even inconsistent (Rao 2001; Terwilliger and Goring 2000). The large amount of linkage data generated from whole-genome screens is difficult to synthesize and interpret.

Both to review the success of the positional cloning paradigm as applied to complex human disease and to investigate the characteristics of the whole-genome scans undertaken to date, we created a database of 101

whole-genome scans of complex human disease, which were found by a systematic Medline search. All studies considered complex diseases in humans, described a complete whole-genome scan (often excluding X and Y chromosomes) and were published in peer-reviewed scientific journals. This database, current as of December 2000, includes the majority of genome scans undertaken in humans to date. We compared these studies, concerning 31 different human complex diseases, with regard to design, methods, and relative "success."

Given the large number of whole-genome scans performed to date—and the concomitant enormous expenditure of research resources—a systematic review of the success and characteristics of such studies seems timely. We hypothesized that such a review might assist researchers to find the appropriate design for their future research work and might also facilitate the evaluation of publications in this field. The principal aims of this study were to review the success of whole-genome scanning as a strategy for gene discovery in complex human disease and to compare and analyze methodical differences related to success in gene localization.

Material and Methods

Database

A database was created containing the following information: publication details (author, title, source, year of study, and main trait); phenotypic traits investigated; study design (environmental factors, number of associated traits, sibling recurrence risk ratio [λ_S], prevalence, ascertainment background, phenotyping procedure, and family structure); details of study population (ethnic background and use of inbred/outbred populations); sample-size details (number of probands, individuals, families, and sib pairs); genotyping methods (type of markers, number of markers, mean polymorphism information content, mean heterozygosity, mean spacing of markers, and missing values); statistical methods; and results obtained (number of positive markers concerning the individual threshold, with localization and marker term; maximum LOD score or *Z* score, and minimum *P* value). When a "second-stage" (e.g., an additional sample of families or additional markers) was reported within the same publication, the database was supplemented with the relevant additional information.

The following initial keywords were used for the search: "genome-wide scan," "genome-wide screen," and "genome-wide search." This entailed the reading and discarding of several thousand titles and several hundreds of abstracts of studies of monogenic diseases or animal models. The search was expanded by use of other terms found to be commonly used in published whole-genome scans (e.g., "susceptibility loci," "genomic scan," and "genome screen"). The database was checked by examination of both the discussion section and the reference list of the publications found in our initial search, allowing the completeness of our database of genome scans in each specific field to be validated. The database was current through the end of December 2000.

Analysis

To investigate study properties that might have been important in determining the relative success or lack of success of the whole-genome scans investigated, it was first necessary to generate some approximate measure of success. The principal outcome variable generated for each study was an ordinal measure of linkage success. For every study, the most significant *P* value for linkage was categorized and coded for analysis, by use of the criteria of Lander and Kruglyak (1995): 0 = no linkage; 1 = suggestive linkage; 2 = significant linkage; 3 = highly significant linkage; and 4 = confirmed linkage (table 1). This measure of "study success" (hereafter referred to as "L-K category") was then used as an ordinal outcome in bivariate and multivariate analyses to determine the best predictors of success among the variables available for each published study.

Sample-size parameters, the number of markers genotyped, the average heterozygozity of genotyped markers, the prevalence, and the λ_S for every disease were analyzed as continuous variables. L-K category and all other variables were analyzed as categorical.

Bivariate analysis used χ^2 tests or Fisher's exact tests (Mehta 1994), for contingency tables or analysis of variance, to compare L-K categories to study parameters of interest. Generalized linear models (logistic regression) (Armitage and Berry 1994) were used to model the effects of multiple covariates on L-K category.

Both forward and backward stepwise modeling procedures were used to select a useful subset of independent predictors of study success. Checks of goodness of fit (McCullagh and Nelder 1989) included an investigation of the need for interaction or polynomial terms, analyses

Table 1

Lander and Kruglyak (1995) Significance Criteria for Mapping of Loci Underlying Complex Traits in Sibs and Half-Sibs

Category	Range of Approximate *P* Values	Range of Approximate LOD Scores
No linkage	1.00–.0008	0–2.1
Suggestive linkage	.0007–.00003	2.2–3.5
Significant linkage	.00002–.0000004	3.6–5.3
Highly significant linkage	⩽.0000003	⩾5.4
Confirmed linkage	Significant linkage in an initial study, confirmed in an independent sample	

of residuals, and examination of the effect of observations with high regression leverage.

SAS version 8 (SAS Institute) was used to construct the initial database. Both SAS version 8 and Splus version 2000 (Mathsoft) were used to manage and analyze data. Statistical significance was defined at the standard 5% level.

Results

1. Descriptive Statistics

Diseases and phenotypes studied.—The 101 studies in our database were performed during 1993–2000, for 31 different complex human diseases (table 2). The most frequently studied diseases were schizophrenia ($n = 10$), type 2 diabetes ($n = 8$), asthma ($n = 7$), bipolar affective disorder ($n = 7$), Crohn disease and inflammatory bowel disease ($n = 7$), psoriasis ($n = 6$), obesity ($n = 5$), prostate cancer ($n = 5$), and type 1 diabetes ($n = 5$). Only four groups of authors published the results of more than one whole-genome scan (Coon et al. 1993, 1994; Ginns et al. 1996, 1998; Ober et al. 1998, 1999, 2000; Lee et al. 2000*a,* 2000*b*). The λ_S and disease prevalence in an appropriate reference population were generally not stated in the articles reporting the whole-genome scans but, for most complex diseases, were available from secondary literature. The λ_S values for the 31 diseases studied were 1.3–75, with two peaks at ~3–4 and ~10–15. The prevalence of the conditions studied in the general population also showed great variation, with a range of 0.04%–40% and a mean of ~4%.

Most studies used disease affection status, coded as a binary (i.e., yes or no) response, as the primary outcome (74% [$n = 75$]). Twelve percent ($n = 12$) of studies used a disease-associated "intermediate" quantitative trait as the primary outcome, and 14% ($n = 14$) of studies used both disease affection status and one or more disease-associated quantitative traits in their linkage analysis.

Study design.—Fifty percent of all studies used an affected-sib-pair design, and 14% used other pairs of affected relatives. Nonaffected relatives (e.g., parents of affected siblings and healthy siblings) were often genotyped also, to increase the information available for calculation of identity-by-descent allele sharing at each marker. In 36% of the studies, extended pedigrees were ascertained.

Families were sampled mainly from outbred (i.e., nonisolated), admixed populations (81% [$n = 81$]). The remaining studies sampled genetically isolated, inbred populations (19% [$n = 19$])—for example, an isolated Finnish subpopulation (Hovatta et al. 1999), U.S. Hutterites (Ober et al. 1998, 1999, 2000), and Old Order Amish (Ginns et al. 1996, 1998)—an approach that assumes reduced heterogeneity both in genetic background and in environmental and lifestyle factors. A study population sampled from a single ethnic group was investigated in the majority (64%) of studies; the remaining studies (36%) sampled from two or more ethnic groups—for example, individuals of European descent, African American, and Hispanic (The Collaborative Study on the Genetics of Asthma 1997).

Sample size.—The study size varied greatly between studies, the range being 20–1,783 individuals comprised by 1–580 families or pedigrees. The varying sample sizes reflected the different ascertainment approaches and study designs and were strongly related to the availability of affected probands in the sampling frames used. There was no significant difference in the mean number of individuals studied, in terms of either year of study or disease studied.

Genotyping methods.—The genotyping methods were the most consistent aspect of the 101 whole-genome screens investigated. All of the whole-genome scans were based on the use of polymorphic microsatellite-marker sets (Reed et al. 1994). There were only a limited number of microsatellite marker sets (e.g., CHLC Weber, Généthon, Research Genetics, and Marshfield) available during the time frame of these studies; markers from these sets were often combined with each other and sometimes were supplemented with specific polymorphic markers or single-nucleotide polymorphisms (SNPs) in putative candidate chromosomal regions. The mean heterozygosity was specified in only 46 studies, and the range was .60–.82. The average spacing between any two microsatellite markers in the whole-genome scans was 4.6–20 cM; the majority of the studies had an average marker spacing of ~11 cM.

Replication of results for specific diseases.—Some diseases were the subject of multiple studies. When these studies and their attained significance levels were compared, it became obvious that it generally is difficult to identify complex human diseases to replicate linkages within them; for example, the number of studies showing no linkage/suggestive linkage/significant linkage/highly significant linkage/confirmed linkage breakdown was 1/5/10/0 for asthma, 3/3/1/0/0 for bipolar affective disorder, 2/2/0/1/1 for psoriasis, 4/4/2/0/0 for schizophrenia, 0/2/1/1/1 for type 1 diabetes, and 0/2/6/0/0 for type 2 diabetes.

Table 3 compares the results of the seven studies of asthma and the eight studies of type 2 diabetes. Highlighting the difficulty of replication in linkage studies of complex human diseases, these studies of asthma and type 2 diabetes reported evidence of linkage on most of the autosomes, and the majority of the reported positive linkages did not overlap (table 3).

Distribution of all "positive" markers.—An average of 4.5 positive loci showing some evidence of linkage, which

Table 2

Characteristics of Whole-Genome Scans for Complex Human Disease ($n = 101$)

Main Trait (Primary Outcome)	Reference(s)	No. of Studies	λ_s
Alcohol dependence (alcoholism and smoking)	Long et al. (1998); Reich et al. (1998)	2	4
Atopy	Ober et al. (1999)	1	1.3
Alzheimer	Pericak-Vance et al. (1997); Kehoe et al. (1999)	2	
Ankylosing spondylitis	Brown et al. (1998)	1	46
Asthma (asthma and atopy)	Daniels et al. (1996), The Collaborative Study on the Genetics of Asthma (1997), Ober et al. (1998, Wjst et al. (1999), Dizier et al. (2000), 2000), Yokouchi et al. (2000)	7	3
Atopic dermatitis	Lee et al. (2000*b*)	1	
Autism	International Molecular Genetic Study of Autism Consortium (1998), Philippe et al. (1999)	2	75
Bipolar affective disorder	Coon et al. (1993), Ginns et al. (1996), McInnes et al. (1996), Adams et al. (1998), Detera-Wadleigh et al. (1999), Morissette et al. (1999), Friddle et al. (2000)	7	15
Blood pressure (hypertension)	Krushkal et al. (1999), Xu et al. (1999), Rice et al. (2000), Sharma et al. (2000)	4	4
Bone-mineral density (osteoporosis)	Devoto et al. (1998), Niu et al. (1999)	2	
Cholesterol concentration (familial combined hyperlipidemia)	Aouizerat et al. (1999), Pajukanta et al. (1999), Rainwater et al. (1999)	3	20
Crohn disease (inflammatory bowel disease)	Hugot et al. (1996), Satsangi et al. (1996), Cho et al. (1998), Hampe et al. (1999), Ma et al. (1999), Duerr et al. (2000), Rioux et al. (2000)	7	35/25
Diabetes:			
Type 1	Davies (1994), Field et al. (1994), Hashimoto et al. (1994), Luo et al. (1995), Mein et al. (1998)	5	15
Type 2 (BMI/age at onset/plasma glucose concentration/prediabetic phenotype)	Hanis et al. (1996), Mahtani et al. (1996), Stern et al. (1996), Hanson et al. (1998), Pratley (1998), Duggirala et al. (1999), Elbein et al. (1999), Hegele et al. (1999), Ehm et al. (2000), Watanabe et al. (2000)	10	4
IgE level, total serum	Xu et al. (2000)	1	
Interphalangeal-joint osteoarthritis	Leppavuori et al. (1999)	1	
Lupus erythematosus	Gaffney et al. (1998), Moser et al. (1998), Shai et al. (1999)	3	15
Mental-health wellness	Ginns et al. (1998)	1	
Multiple sclerosis	Ebers et al. (1996), Haines et al. (1996), Sawcer et al. (1996), Kuokkanen et al. (1997)	4	30
Obesity, energy metabolism, leptin variation	Comuzzie et al. (1997), Hager et al. (1998), Norman et al. (1998), Lee et al. (1999), Ohman et al. (2000)	5	4
Open-angle glaucoma	Wiggs et al. (2000)	1	8
Osteoarthritis	Chapman et al. (1999)	1	23
Panic disorder	Knowles et al. (1998)	1	8
Pre-eclampsia (eclampsia)	Harrison et al. (1997), Arngrimsson et al. (1999)	2	
Prostate cancer (aggressive prostate cancer)	Smith et al. (1996), Berthon et al. (1998), Gibbs et al. (1999), Suarez et al. (2000), Witte et al. (2000)	5	3
Psoriasis	Tomfohrde et al. (1994), Matthews et al. (1996), Nair et al. (1997), Trembath et al. (1997), Samuelsson et al. (1999), Lee et al. (2000*a*)	6	7
Raynaud phenomenon	Susol et al. (2000)	1	
Rheumatoid arthritis	Cornelis et al. (1998), Shiozawa et al. (1998)	2	5/8
Schizophrenia	Coon et al. (1994), Moises et al. (1995), Blouin et al. (1998), Faraone et al. (1998), Kaufmann et al. (1998), Levinson et al. (1998), Shaw et al. (1998), Hovatta et al. (1999), Williams et al. (1999), Ekelund et al. (2000)	10	10
Testicular tumor	Leahy et al. (1995), Rapley et al. (2000)	2	9
Tuberculosis	Bellamy (2000)	1	

were chosen on the basis of different individual thresholds, were reported in every study. These 453 "hits" were not distributed equally among all 23 chromosomes.

We plotted the observed hit ratio (%: hits on every chromosome/all 453 hits) against an expected hit ratio (%: genes on every chromosome/all 37,701 genes of the genome, when chromosome sizes and gene content are rated as suggested by Venter et al. [2001]). The linear regression suggested a close correlation between the expected hit ratio and the observed hit ratio (fig. 1). This suggests that the null hypothesis of random linkages across the genome cannot be rejected, since all the whole-genome scans investigated used markers (roughly) equally distributed across the genome and a close association of the positive linkages with theoretical gene-content could be shown.

However, chromosomes 4, 6, and 16 showed an increased observed hit ratio, relative to the expected hit ratio. This may indicate the presence of one or more pleiotropic loci encoding susceptibility for multiple diseases and traits. Markers in or near the HLA locus on chromosome 6p, for example, show some evidence of linkage to type 1 diabetes (Davies et al. 1994; Field et al. 1994; Hashimoto et al. 1994; Mein et al. 1998), multiple sclerosis (Haines et al. 1996; Kuokkanen et al. 1997), rheumatoid arthritis (Cornelis et al. 1998), psoriasis (Nair et al. 1997; Trembath et al. 1997; Samuelsson et al. 1999; Lee et al. 2000*a*), inflammatory bowel (Hampe et al. 1999; Rioux et al. 2000), and asthma/allergy (Daniels et al. 1996; The Collaborative Study on the Genetics of Asthma 1997; Ober et al. 1999; Wjst et al. 1999).

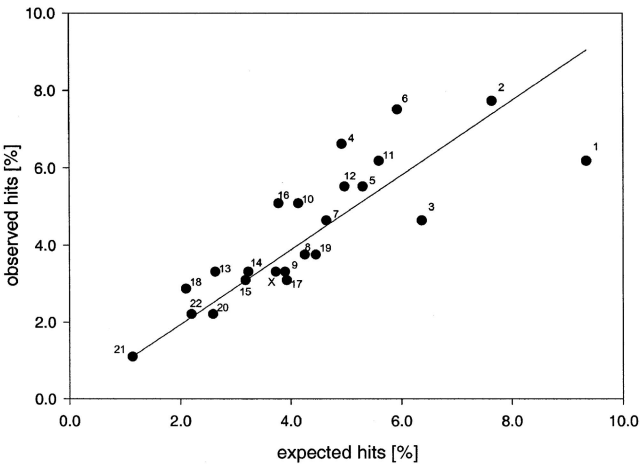

Figure 1 Regression analysis of expected and observed hits on chromosomes 1–22 and X. An average of 4.5 "positive" loci showing some evidence of linkage, chosen by different individual thresholds, were reported in every study. The observed hit ratio (%: hits on every chromosome/all 453 hits) is plotted against the expected hit ratio (%: genes on every chromosome/all 37,701 genes of the genome, when chromosome sizes and gene content are rated as suggested by Venter et al. [2001]).

2. *Analysis*

Many different linkage-analysis techniques and models (e.g., model-based and model-free methods, two-point

Table 3

Comparison of Loci Found in Studies of Asthma and Type 2 Diabetes

Disease and Reference	Study Design	No. of Individuals Genotyped	Significance Level[a]	Chromosome(s) for Which Positive Findings Were Reported
Asthma:[b]				
Daniels et al. (1996)	Sib pair	364	Suggestive linkage	4, 6, 7, 11, 13, 16
The Collaborative Study on the Genetics of Asthma (1997)	Sib pair	540	Suggestive linkage	2, 5, 6, 11–14, 17, 19, 21
Ober et al. (1998)	Extended pedigree	361	Suggestive linkage	2, 3, 5, 9, 12, 13, 19, 21
Wjst et al. (1999)	Sib pair	415	No linkage	2, 6, 9, 12
Dizier et al. (2000)	Sib pair	211	Suggestive linkage	1, 11–13, 17, 19
Ober et al. (2000)	Extended pedigree	693	Suggestive linkage	5, 8, 14, 16, 19
Yokouchi et al. (2000)	Sib pair	197	Significant linkage	4, 5, 13
Type 2 diabetes:[c]				
Hanis et al. (1996)	Sib pair	408	Significant linkage	2
Mahtani et al. (1996)	Extended pedigree	217	Significant linkage	12
Hanson et al. (1998)	Affected relatives	656	Suggestive linkage	11
Duggirala et al. (1999)	Extended pedigree	440	Significant linkage	3, 4, 9, 10
Elbein et al. (1999)	Extended pedigree	468	Significant linkage	1
Hegele et al. (1999)	Sib pair	33	Significant linkage	3, 6, 8, 10, 16, 22
Ehm et al. (2000)	Affected relatives	1,783	Significant linkage	3, 5, 10, 12, X
Ghosh et al. (2000)	Sib pair	1,438[d]	Suggestive linkage	

[a] Defined on the basis of the criteria of Lander and Kruglyak (1995).
[b] There were 42 linkage hits on 17 different chromosomes—3 each on chromosomes 5, 12, and 19 and 5 on chromosome 13.
[c] There were 25 linkage hits on 15 different chromosomes—3 on chromosome 3 and 4 on chromosome 10.
[d] 719 sib pairs.

Table 4

Relationship of Study Variables to Study Success

Variable	No Linkage	Suggestive Linkage	Significant Linkage	Highly Significant Linkage	Confirmed Linkage
	Proportion (No.) of Studies Successful[a]				
Ascertainment:					
Affected sib pairs	21.6% (11)	45.1% (23)	23.5% (12)	7.8% (4)	2.0% (1)
Affected relative pairs	7.1% (1)	50.0% (7)	35.7% (5)	.0%	7.1% (1)
Extended pedigrees	22.2% (8)	47.2% (17)	27.8% (10)	2.8% (1)	.0%
Population:					
Outbred, admixed	19.5% (16)	45.1% (37)	26.8% (22)	6.1% (5)	2.4% (2)
Inbred, isolated	21.0% (4)	52.6% (37)	26.3% (5)	.0%	.0%
Primary outcome investigated:					
Qualitative	34.0% (18)	38.7% (29)	28.0% (21)	6.7% (5)	2.7% (2)
Quantitative	8.3% (1)	83.3% (10)	8.3% (1)	.0%	.0%
Qualitative and quantitative	7.1% (1)	57.1% (8)	35.7% (5)	.0%	.0%
No. of ethnic groups studied:					
One	16.4% (10)	42.6% (26)	29.5% (18)	8.2% (5)	3.3% (2)
More than one	22.9% (8)	54.3% (19)	22.9% (8)	.0%	.0%
	Mean (SE)				
No. of families studied	75.8 (17.7)	92.4 (16.3)	97.9 (18.6)	112.8 (43.2)	68.5 (27.5)
No. of individuals studied	243.9 (38.5)	393.6 (49.2)	470.5 (69.4)	435.0 (189.0)	331.0 (69.0)
Disease prevalence (%)	4.0 (1.6)	5.2 (1.4)	3.4 (.8)	1.1 (.6)	1.1 (.8)
λ_S	15.1 (10.0)	12.3 (2.2)	12.1 (2.3)	20.2 (7.2)	11.0 (4.0)

[a] Success measures are L-K categories.

and multipoint linkage analysis, and variance-components and regression-based methods) were used within the available software packages. LOD scores and *Z* scores were transformed into asymptotic *P* values, if these were not already listed.

When classification on the basis of L-K category was used, 4% ($n = 4$) of the whole-genome scans showed highly significant linkage, 24% ($n = 23$) showed significant linkage, 47% ($n = 44$) showed suggestive linkage, and the remaining 24% ($n = 23$) showed little (often referred to as "nominal" linkage). Forty-one studies reported more than one "stage" in the same publication. A "second stage" genome screen generally involved either a second whole-genome scan, the typing of selected markers on a second sample of families, in an attempt to replicate the positive findings of the initial genome scan, or the typing of a denser marker set ("flanking markers") in certain regions in the same sample of families. Approximately half of these second stages led to an improvement in the statistical significance of individual linkages. The reporting of these second-stage approaches in some of the reviewed studies made it necessary to redefine study success, beyond what each article simply reported for the initial (first-stage) "genomewide-scan result." This "overall study result" was used as the primary outcome in our analyses and considers the lowest *P* value attained either in one of the study stages or in the combined sample data. When classification on the basis of L-K category was used, 2% ($n = 2$) of the studies showed confirmed linkage, 5% ($n = 5$) showed highly significant linkage, 27% ($n = 27$) showed significant linkage, 46% ($n = 47$) showed suggestive linkage, and 20% ($n = 20$) showed no linkage.

Bivariate analysis.—Bivariate analysis found no significant association between study success, as defined by L-K category, and the following study parameters (table 4): ascertainment (Fisher's exact test; $P = .21$); population studied—either inbred/outbred (Fisher's exact test; $P = .92$) or one ethnic group/more than one ethnic group (Fisher's exact test; $P = .28$); primary outcome investigated (qualitative/quantitative/both) (Fisher's exact test; $P = .23$); number of families studied ($F_{4,93} = 0.22$; $P = .92$); number of individuals studied ($F_{4,94} = 1.52$; $P = .20$; see fig. 2); disease prevalence ($F_{4,88} = 0.61$; $P = .66$); and λ_S ($F_{4,78} = 0.48$; $P = .75$; see fig. 3). However, the following variables showed some trend toward an association with higher L-K category (table 4): study of only one ethnic group; number of individuals studied (fig. 2); and study of an outbred population.

Multivariate analysis.—Ordinal logistic regression suggested that both the number of individuals studied (odds ratio = 1.004/subject, 95% confidence interval = 1.001–1.008; $P = .03$) and the study of one ethnic group (vs. multiple ethnic groups) (odds ratio = 2.44, 95% confidence interval = 1.08–5.54; $P = .03$) were associated with increased study success. These associations were independent of (1) the specific disease studied, (2) the type of trait investigated as the primary outcome, (3) the ascertainment method, (4) either λ_S or the population prevalence of the condition studied, or (5) statistical test used.

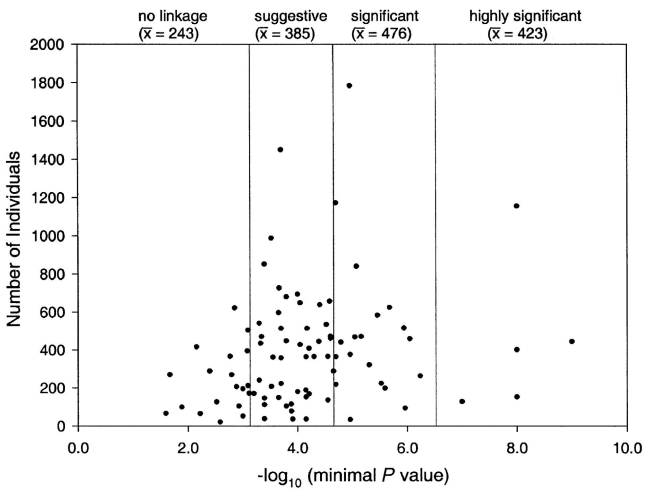

Figure 2 Number of individuals, plotted against minimum attained *P* value. The correlation of sample size and study "success" in the genome scans reviewed is illustrated. The vertical lines correspond to the significance thresholds suggested by Lander and Kruglyak (1995), and the mean number of individuals studied in each category is shown.

Discussion

Our review was designed to compare 101 whole-genome scans in 31 different diseases, in terms of design, methods, and success. Studies varied widely with regard to study design and statistical analysis. Most studies did not show significant linkage when the criteria of Lander and Kruglyak (1995) were used. The findings in studies of the same disease are often inconsistent; the number of observations of highly significant and confirmed linkages is very small, and unequivocal statements are difficult to make.

Although this review has focused on one dimension of the success of whole-genome scans, it is important to remember that the underlying purpose of such studies is to discover susceptibility loci for a complex disease—the real success of a whole-genome scan is unlikely to be defined solely by the minimum attained *P* value of the linkage analysis. Potential publication bias was ignored in our review. There are a number of genome scans of complex human diseases, known to have been undertaken by private industry, that have not been published. The involvement of commercial enterprises in gene-discovery attempts has put a premium on secrecy, and the results of these genome scans could not be included in this review. There has been no systematic assessment of publication bias in whole-genome screens, and such an undertaking was beyond the scope of our review. However, the lack of evidence of a correlation between year of publication and study success suggests that this was not an important bias in the sample of whole-genome screens surveyed. A further potential bias in our study relates to the way in which the Medline search was undertaken. Validation of our database by the discussions and reference lists in primary literature discovered in an initial Medline search may have led to the inclusion of a disproportionate number of the genome scans of the more frequently investigated diseases.

The use of Lander and Kruglyak's (1995) proposed categorizations as an approximate measure of study success is somewhat arbitrary and could have biased our study in unknown ways. In their article, Lander and Kruglyak (1995) argue strongly for the value of such categorizations, and their scheme has been adopted by many researchers. However, to ensure that our categorization of success had not biased our study, we also repeated our analyses, using, as a continuous outcome, $-\log_{10}$ (minimum *P* values) from each study. The results were very similar to those reported when the L-K categories (data not shown) were used, suggesting that the use of this categorization scheme did not result in any significant bias.

Our analysis suggests that sample size is an important determinant of study success. Possibly because the extended-pedigree approach has low numbers of families and proportionally higher numbers of individuals, the number of individuals studied proved to be the most informative index of sample size. The most obvious differences in study success that were due to sample size were observed for the difference between no linkage and any evidence of suggestive or better linkage (fig. 2); on average, studies that, by Lander and Kruglyak (1995)

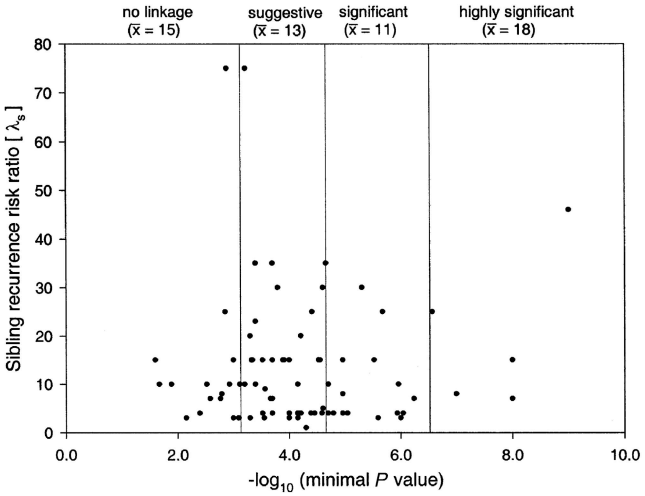

Figure 3 λ_S, Plotted against minimum attained *P* value. The correlation of λ_S and study "success" in the genome scans reviewed is illustrated. The vertical lines correspond to the significance thresholds suggested by Lander and Kruglyak (1995), and the mean λ_S in each category is shown.

criteria, showed suggestive linkage had twice the sample size (number of individuals) of studies showing no evidence of linkage.

The study of a sample selected from a single ethnic group also appeared to be advantageous with regard to L-K category attained. This may be due both to the increase in heterogeneity in the study sample, occasioned by introduction of samples from different ethnic groups, and to the current general lack of appropriate statistical methodology to assess or adjust for the resulting increased heterogeneity.

It has been proposed that, compared with outbred, admixed populations, genetically isolated populations may offer some advantages for the mapping of complex genetic traits (de la Chapelle 1993; Jorde 1995). However, both in contrast to the theoretical advantages to the use of inbred populations position and in accord with some recent statistical concerns (Lonjou et al. 1999), the empirical data show that studies using such populations are, on average, no more successful than studies using samples from general, outbred populations. This finding may be the result of factors such as either the lack of availability of an available inbred population for study of a particular disease or, possibly, to disadvantages inherent in an extended-pedigree approach.

Rare diseases are generally more difficult to investigate in a large study, since (*a*) study design is often limited by the number of available samples and (*b*) collecting a large number of families containing one or more affected individuals can be problematical. However, our review suggests that there is no identifiable disadvantage associated with the study of rarer complex diseases compared with more-common diseases.

It has been generally accepted that quantitative "intermediate" phenotypes, when available, are likely to be more objective and informative—and, hence, more statistically powerful—and hence preferable to dichotomous disease affection outcomes (Amos and Laing 1993). However, our analyses do not suggest that, as outcomes for linkage analysis, quantitative traits have any important advantages over qualitative traits. Given that many different diseases were studied by many disparate methods, it is difficult to ascribe meaning to this finding. Possibly the intraindividual fluctuations over time, as well as difficulties in consideration of covariate adjustment for quantitative intermediate phenotypes may bias the phenotypes, introducing noise into the linkage analysis.

λ_S is a variable that characterizes the familial aggregation of a disease; the λ_S value can be used to estimate the power that affected-sib-pair methods have to detect linkage (Risch 1990). Whole-genome scans have succeeded in the analysis of monogenic traits, which tend to have extremely high estimated λ_S values (Farrer and Cupples 1998). The results of gene mapping in monogenic disease, together with theoretical studies of λ_S values (Risch 1990), suggest that genes for complex diseases with a relatively high λ_S may be more easily localized. However, our results are not consistent with this theoretical expectation (fig. 3). This finding calls into question whether the λ_S measure has utility for linkage studies of common, complex human diseases.

The comparison of variables related to study design and power vis-à-vis the best L-K category attained in every study may only suggest some more-obvious trends and does not prove that the observed differences are critical to success. Our results suggest that, beyond the almost tautological finding that larger samples and reduced heterogeneity are better, there is no gold standard applicable to complex human diseases. One recommendation that we do feel confident to make is that, in publications of whole-genome scans, more-careful attention should be paid to the characterization of both the methods (particularly the ascertainment and the phenotyping procedures) and the results. Undertaking our review was made extremely difficult by the inconsistency of the studies reviewed, in terms of their reporting of methods and results; a degree of subjective interpretation was often necessary in order to identify all of the relevant parameters from a study. Linkage results were sometimes presented primarily as LOD-score or *P*-value diagrams (often small and hard to read) for each chromosome. Very few studies gave any information regarding marker informativity, making it impossible to study this parameter. Detailed descriptions of methodology (particularly for studies involving multiple stages) and the reporting of maximum LOD scores and/or minimum *P* values in tabular form (in addition to or instead of graphic representations) would much improve the situation. There is a lack of generally accepted criteria for replication of linkage results; it remains unclear exactly what constitutes "replication" in a genome scan. For the purposes of our review, we took reported replication at face value, even though this may involve different criteria (e.g., within 10 cM vs. within 5 cM) in different studies. Finally, as Lander and Kruglyak (1995) argue, ideally every individual whole-genome screen would report empirically determined significance criteria *for that study.* These problems are as much the fault of journal editors as they are of individual authors, and they need to be addressed by comprehensive, uniform guidelines.

The whole-genome screens for complex human disease that have been reviewed here have a number of important limitations. Sample sizes were generally modest; the relatively small numbers studied would have (*a*) tended to limit the power of these genome screens to detect linkage and (*b*) increased the possibility of type I experimental error (Terwilliger and Goring 2000). The use of widely differing significance thresholds within each sample make it difficult to compare them. In most of the studies, no replication of putative novel linkages

has yet been attempted in independent population samples of similar ethnicity. Furthermore, the (often tacit) assumption that the susceptibility genes for quantitative traits associated with disease affection will be equivalent to the susceptibility genes for the disease in question may not necessarily be valid. However, it is easy to be critical in hindsight, and it is important to recognize that these studies are embedded within a historical matrix; the many difficulties inherent in positional cloning have become apparent only through the experience gained during the past decade.

What Studies That Showed Highly Significant or Confirmed Linkage Have in Common

Five studies showed one or more highly significant linkages, and two showed confirmed linkage (Davies et al. 1994; Field et al. 1994; Tomfohrde et al. 1994; Satsangi et al. 1996; Trembath et al. 1997; Brown et al. 1998; Shiozawa et al. 1998). All seven of these studies used a qualitative main trait (in two studies of type 1 diabetes, one study of rheumatoid arthritis, one study of ankylosing spondylitis, one study of inflammatory bowel disease, and two studies of psoriasis) and sampled from outbred populations, and five of them used a sib-pair approach. Were these results obtained by chance (a "lucky" search for the right trait in the right families), or do these studies have something else in common? Although a significant relationship between sample size and attained significance level could be demonstrated, the most-significant results were not achieved by the largest studies in this group. No clear strategy for success could be delineated by our review, except perhaps a preference for autoimmune diseases. The success of studies of such diseases may reflect both an increased genetic component of variance and reduced locus heterogeneity, relative to the other diseases investigated. Study design also may have played a role; the selection of families was generally undertaken with the aim of focusing either on a well-defined subtype of the disease or on large pedigrees in which the disease appeared to exhibit Mendelian inheritance (e.g., see Tomfohrde et al. 1994; Brown et al. 1998).

For type 1 diabetes, larger numbers of families were collected (Davies et al. 1994; Field et al. 1994), and both studies of this disease reported that their best linkage results were for markers in the HLA region on chromosome 6p21. This locus also was found in other studies of type 1 diabetes (Hashimoto et al. 1994; Mein et al. 1998). These findings suggest that, at least in some diseases, the positional-cloning paradigm holds true—that is, an important locus can be found and replicated.

Future Directions

Although, during the past decade, significant progress has been made in defining the genetic basis of complex human diseases, even relatively large studies are likely to have had low power to map, by linkage, genes of modest effect (Risch 2000; Terwilliger and Goring 2000). One potential solution to this and other issues is to combine data from multiple studies. Meta-analysis is an emerging methodology in the linkage analysis of complex-disease genetics (Morton 1995; Rice 1997; Gu et al. 1998; Xu and Meyers 1998; Badner and Goldin 1999; Guerra et al. 1999; Wise and Lewis 1999); the combination of evidence from multiple studies may prove to be critical to the successful localization of genes of modest effect in common complex human diseases (Palmer et al. 2001*a,* 2001*c;* The Transatlantic Multiple Sclerosis Genetics Cooperative 2001).

Our results suggest that some elements of study design are likely to be important in the determination of the relative success of a whole-genome scan. Every individual study and disease is likely to require an optimized study design that takes into account the unique characteristics of both that sample and the phenotypes studied (Terwilliger and Goring 2000). Our review suggests that attention to maximization of sample homogeneity is likely to be particularly important. Unfortunately, this cart is often placed a long distance before the horse: linkage analysis is very often attempted *before* appropriate descriptive analyses—to allow informed study design and genetic analysis in the sampling frame in question—are undertaken to determine the interrelationships of the phenotypes and covariates being studied; for example, although asthma has been the subject of many genome scans (table 3), only recently have the interrelationships between the underlying genetic determinants of intermediate phenotypes begun to be investigated (Palmer et al. 2000, 2001*b*). It is to be hoped that the recent advent of cheaper and improved computing power, together with methodological advances in complex modeling techniques (e.g., see Zeger and Karim 1991), will lead to the continuing development and application of new computing-intensive statistical methodologies that are ideal for complex genetic modeling. Finally, an understanding of the genetic epidemiology of many diseases would be greatly enhanced by population-based studies. Such studies, although expensive and difficult to undertake, are the foundation of good genetic epidemiology and address many important epidemiological issues, such as generalization (Hopper et al. 1999).

Conclusions

Gene discovery in complex human disease has been complicated by substantial etiological heterogeneity, the possibility of genes of small effect, and the concomitant requirement for large samples. The mapping of human susceptibility loci for such diseases may be made difficult by any or all of the following: high population frequency, incomplete penetrance, phenocopies, genetic heterogeneity, possible epistasis, and pleiotropy (Weeks and Lathrop

1995); replication of any positive results may be difficult, and often the significance of studies' different findings is controversial. As a consequence, the application of linkage analysis to complex disorders without obvious Mendelian inheritance has had limited success thus far.

Genetic approaches to complex diseases offer great potential to improve our understanding of the pathophysiology of these disorders, but they also offer significant challenges. Although the past decade made great progress in defining the genetic basis of such diseases, accompanied by rapid technical progress in genotyping technologies and statistical methodology, further research is required, especially in the area of study design. In particular, the genetic localization of most susceptibility loci is still insufficiently precise for the positional cloning of new genes influencing disease. There have been linkages reported on nearly every autosome, in multiple whole-genome screens for the same disease, and the sheer number of "consensus regions" identified by such screens highlights the difficulty of positional-cloning attempts in common complex diseases such as asthma and diabetes (Lander and Schork 1994; Palmer and Cookson 2000). Whether positional cloning based on whole-genome screens ultimately delivers on its promises for complex human diseases remains to be seen. It may be that high-density SNP association analysis in combination with functional genomic data may prove to be necessary to detect susceptibility loci (which may be of small effect) for many complex human diseases (Risch 2000). In the meantime, like true love, true linkage remains hard to find.

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